Table 2
The ten SNPs were analyzed for all subjects ($n=93$) except for PAI-1 4G/5G ($n=90$) and PPARα Leu162Val ($n=91$).

Type of SNP	Distribution of different genotypes			Total n
Factor V Leiden	93 [GG; Arg/Arg]	0 [AG; Gln/Arg]	0 [AA; Gin/Gin]	[93]
Prothrombin G20210A	93 [GG]	0 [AG]	0 [AA]	[93]
Factor XIII Val34Leu	93 [GG; Val/Val]	0 [TG; Leu/Val]	0 [TT; Leu/Leu]	[93]
Factor VII Arg353Gln	81 [GG; Arg/Arg]	11 [AG; Gln/Arg]	1 [AA; Gln/Gln]	[93]
MTHFR C677T	35 [CC; Ala/Ala]	39 [TC; Val/Ala]	19 [TT; Val/Val]	[93]
β-fibrinogen G-455A	73 [GG]	19 [AG]	1 [AA]	[93]
PAI-1 4G/5G	9 [5G/5G]	41 [4G/5G]	40 [4G/4G]	[90]
PPARα Leu162Val	91 [CC; Leu/Leu]	0 [GC; Val/Leu]	0 [GG; Val/Val]	[91]
eNOS Glu298Asp	80 [GG; Glu/Glu]	12 [TG; Asp/Glu]	1 [TT; Asp/Asp]	[93]
ERα IVS1-401	13 [CC]	44 [TC]	36 [TT]	[93]

For example, '0 [AG; Gln/Arg]' indicates that the genotype is an A and G allele heterozygous genotype coding for Gln and Arg, with $n=0$ subjects. SNP, single nucleotide polymorphism; G, guanine; A, adenine; T, thymine; C, cytosine; Arg, arginine; Gln, glutamine; Val, valine; Leu, leucine; Ala, alanine; Glu, glutamic acid; Asp, aspartic acid; IVS, intervening sequence.

dichotomized by the demarcation line. A probability value under 0.05 as determined by two-tail analyses was considered statistically significant.

Results

Study population and genotype distribution

The patient profiles are shown in Table 1. The observed population contains clinical backgrounds such as the following with some holding multiple diseases; angina ($n=3$), arteriosclerosis ($n=2$), cardiac insufficiency ($n=5$), cerebrovascular accident which contains a sequela ($n=19$), diabetes ($n=11$), hyperlipemia ($n=14$), hypertension ($n=42$), and none disease carriers ($n=28$) (supplemental Table 1b). The distribution of the different genotypes for each of the ten analyzed SNPs is shown in Table 2. As suggested in the introduction, we confirmed that neither prothrombin G20210A nor factor V Leiden was present at detectable levels in our samples. Genotype frequencies were in Hardy–Weinberg equilibrium for all the SNPs, analyzed by chi-square test on observed versus expected genotype frequencies (all $P>.05$) (supplemental Table 2b). We proceeded with dominant model analyses to investigate the relation of genotypes to clinical values, and those which appeared to have significant differences are further addressed.

Table 3
All variables are presented as mean ± SEM.

Characteristic	GG [$n=81$; 87.1%]	AG+AA [$n=12$; 12.9%]	P-value [GG vs. AG+AA]
Age, years	81.04 ± 1.00	80.33 ± 1.82	.795
Total cholesterol, mg/dL	207.75 ± 5.16	195.50 ± 8.24	.373
LDL-C, mg/dL	119.10 ± 6.07	131.19 ± 7.15	.337
HDL-C, mg/dL	59.44 ± 2.24	47.93 ± 3.85	.049*
Triglycerides, mg/dL	111.34 ± 6.12	125.42 ± 13.85	.380
Creatinine, mg/dL	0.84 ± 0.03	0.80 ± 0.04	.736
BNP, pg/mL	78.81 ± 9.04	69.97 ± 17.57	.681
Glucose, mg/dL	98.11 ± 3.82	108.00 ± 8.51	.370
TNF-α, pg/mL	3.91 ± 0.35	4.22 ± 0.66	.721
IL-6, pg/mL	7.32 ± 2.40	5.80 ± 1.91	.788
cGMP, pmol/mL	7.47 ± 0.45	6.30 ± 0.85	.299
NOx, μmol/L	52.56 ± 4.11	70.27 ± 12.16	.106
Hemoglobin, g/dL	11.92 ± 0.22	11.58 ± 0.65	.645

$P<.05$ is indicated by an asterisk (*). Mann–Whitney U-tests were performed on HDL-C, Creatinine, BNP, and cGMP values, while unpaired Student's t-tests were used for the other values. Of note, GG [$n=71$] and AG+AA [$n=12$] for triglycerides, and GG [$n=37$] and AG+AA [$n=5$] for glucose were analyzed. The G/A allele codes for Arg/Gln. Arg, arginine; Gln, glutamine; G, guanine; A, adenine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; cGMP, cyclic guanosine 5'-monophosphate; NOx, nitric oxide metabolites.

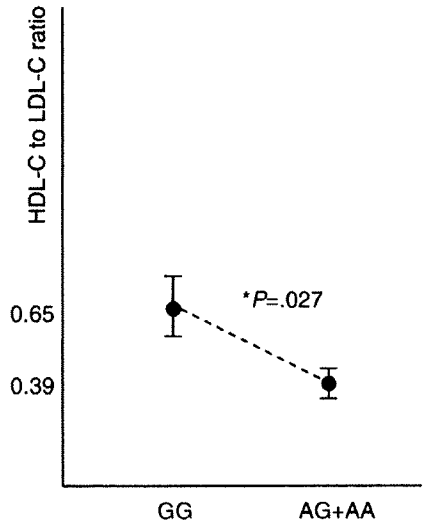

Fig. 1. Genotype affects the HDL-C to LDL-C ratio. The Mann–Whitney U-test was performed on factor VII Arg353Gln genotypes vs. HDL-C to LDL-C ratio. $P<.05$ is indicated by an asterisk (*). Bar indicates SEM. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; G, guanine; A, adenine; Arg, arginine; Gln, glutamine.

Factor VII gene polymorphism and HDL-C

As shown in Table 3, the factor VII Arg353Gln polymorphism was linked to HDL-C. The GG genotype encoding for Arg/Arg was associated with higher HDL-C levels than the AG+AA genotypes ($P=.049$). This finding is supported by comparison of the HDL-C to LDL-C ratio for the GG genotype (0.65 ± 0.10) and the AG+AA genotypes (0.39 ± 0.05), which were significantly different ($P=.027$) (Fig. 1). We did not observe a significant difference among LDL-C levels between genotypes, although there was a similar trend.

Endothelial nitric oxide synthase gene polymorphism and triglycerides

As shown in Table 4, the eNOS Glu298Asp polymorphism was related to triglycerides. The GG genotype encoding for Glu/Glu was associated with higher triglyceride levels than the TG+TT genotypes

Table 4
All variables are presented as mean ± SEM.

Characteristic	GG [$n=80$; 86.0%]	TG+TT [$n=13$; 14.0%]	P-value [GG vs. TG+TT]
Age, years	80.48 ± 1.00	83.85 ± 1.61	.195
Total cholesterol, mg/dL	208.24 ± 4.82	192.25 ± 14.85	.244
LDL-C, mg/dL	122.80 ± 4.14	105.79 ± 18.66	.351
HDL-C, mg/dL	57.73 ± 2.29	59.03 ± 3.45	.837
Triglycerides, mg/dL	117.82 ± 6.00	80.90 ± 11.47	.031*
Creatinine, mg/dL	0.84 ± 0.03	0.80 ± 0.11	.767
BNP, pg/mL	73.79 ± 8.28	101.60 ± 28.74	.240
Glucose, mg/dL	99.80 ± 3.57	n.a.	n.a.
TNF-α, pg/mL	4.02 ± 0.34	3.71 ± 0.80	.702
IL-6, pg/mL	5.81 ± 1.70	12.65 ± 8.14	.195
cGMP, pmol/mL	7.19 ± 0.42	7.67 ± 1.14	.648
NOx, μmol/L	57.00 ± 4.79	48.40 ± 4.82	.405
Hemoglobin, g/dL	11.95 ± 0.22	11.43 ± 0.66	.452

$P<.05$ is indicated by an asterisk (*). Mann–Whitney U-tests were performed on LDL-C and creatinine values, while unpaired Student's t-tests were used for the other values. Of note, GG [$n=73$] and TG+TT [$n=10$] for triglycerides, and GG [$n=41$] and TG+TT [$n=1$] for glucose were analyzed. Since the latter separated as TG+TT [$n=1$], analyses were not performed (n.a.). The G/T allele codes for Glu/Asp. Glu, glutamic acid; Asp, aspartic acid; G, guanine; T, thymine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; cGMP, cyclic guanosine 5'-monophosphate; NOx, nitric oxide metabolites.

($P=.031$). Since triglycerides is a clinical marker with an accepted demarcation line, that is 100 mg/dL, we used the chi-square test to assess whether the GG genotype and TG+TT genotypes has or has not had an effect on triglyceride levels dichotomized by this line. As shown in Fig. 2, genotype does not influence the demarcation line but has an effect on the triglyceride levels ($P=.021$).

Estrogen receptor alpha gene polymorphism and BNP

As shown in Table 5, the ERα IVS1-401 polymorphism was related to the plasma BNP concentration, with the CC genotype being associated with a relatively lower plasma BNP concentration when compared to the TC+TT genotypes ($P=.031$). Since BNP is a standard clinical marker for heart failure with a well-known demarcation line, that is 80 pg/mL, we used the chi-square test to assess whether the CC genotype and TC+TT genotypes has or has not had an effect on BNP levels dichotomized by this line. As shown in Fig. 2, it was revealed that genotype does not influence the demarcation line but has an effect on the BNP levels ($P=.031$).

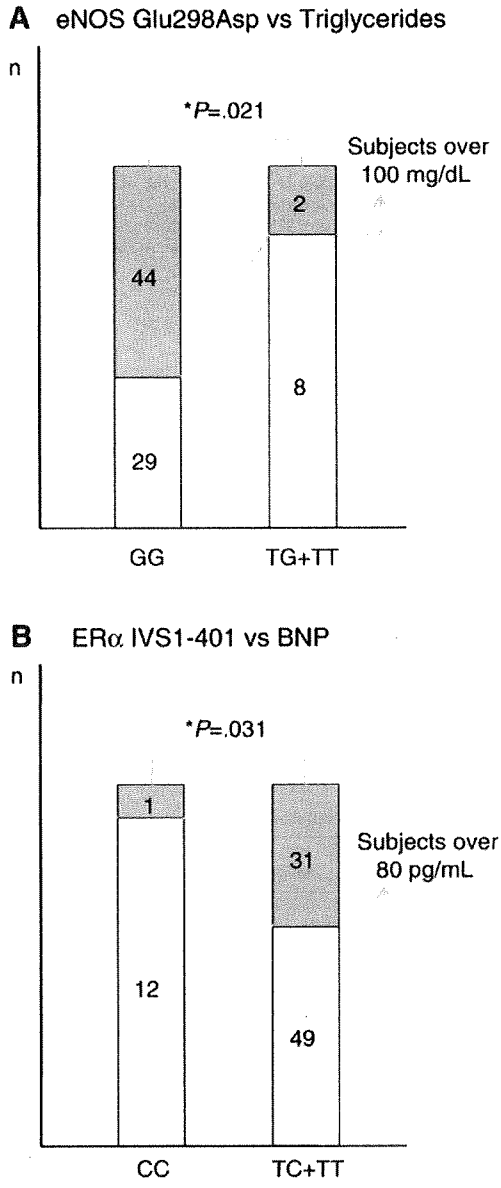

Fig. 2. The eNOS and ERα genotypes influence the concentration of triglycerides and BNP. Chi-square tests were done on eNOS Glu298Asp genotypes vs. triglyceride concentration separated by 100 mg/dL (A), and on ERα IVS1-401 genotypes vs. BNP concentration separated by 80 pg/mL (B). The gray box above the dotted line indicates the number of subjects who were over the demarcation line. $P<.05$ is indicated by an asterisk (*). Each box was sized to reflect the percentage for visual purposes. Glu, glutamic acid; Asp, aspartic acid; G, guanine; T, thymine; IVS, intervening sequence; BNP, B-type natriuretic peptide; C, cytosine.

Table 5
All variables are presented as mean ± SEM.

Characteristic	CC [$n=13$; 14.0%]	TC+TT [$n=80$; 86.0%]	P-value [CC vs. TC+TT]
Age, years	79.31 ± 3.10	81.21 ± 0.92	.466
Total cholesterol, mg/dL	211.62 ± 11.37	205.22 ± 5.07	.631
LDL-C, mg/dL	128.81 ± 9.81	119.62 ± 4.68	.486
HDL-C, mg/dL	62.96 ± 7.57	57.19 ± 2.10	.362
Triglycerides, mg/dL	115.64 ± 11.67	113.03 ± 6.23	.876
Creatinine, mg/dL	0.82 ± 0.06	0.84 ± 0.03	.804
BNP, pg/mL	52.17 ± 19.69	81.82 ± 8.90	.031*
Glucose, mg/dL	102.80 ± 10.57	98.81 ± 3.78	.719
TNF-α, pg/mL	4.90 ± 1.02	3.74 ± 0.31	.149
IL-6, pg/mL	5.02 ± 1.56	7.55 ± 2.48	.633
cGMP, pmol/mL	6.53 ± 0.90	7.44 ± 0.45	.384
NOx, μmol/L	54.14 ± 6.48	55.64 ± 4.67	.889
Hemoglobin, g/dL	12.27 ± 0.74	11.82 ± 0.20	.411

$P<.05$ is indicated by an asterisk (*). Mann–Whitney U-tests were done on HDL-C, creatinine, BNP and cGMP values, while unpaired Student's t-tests were used for the other values. Of note, CC [$n=11$] and TC+TT [$n=72$] for triglycerides, and CC [$n=5$] and TC+TT [$n=37$] for glucose were analyzed. IVS, intervening sequence; C, cytosine; T, thymine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; cGMP, cyclic guanosine 5'-monophosphate; NOx, nitric oxide metabolites.

Discussion

We restricted our subjects to postmenopausal elderly women (with a mean age of 80.9 years) who were free of factor V Leiden and prothrombin G20210A. In doing so, we were able to identify new correlations between the factor VII Arg353Gln polymorphism and HDL-C levels, and between the eNOS Glu298Asp polymorphism and triglyceride levels. We have demonstrated, for the first time, a statistically significant association between the ERα IVS1-401 polymorphism and plasma BNP concentration, suggesting that CC genotype carriers have relatively lower plasma BNP levels than TC+TT genotypes ($P=.031$). To our knowledge, there are no other reports linking the heart failure marker BNP with an SNP in the estrogen system.

Recently, an important meta-analysis of HRT ruled out the possibility that HRT increases HDL-C and reduces either LDL-C or the LDL-C to HDL-C ratio (Salpeter et al. 2006). Concerning SNPs, a recent meta-analysis implied that the ERα IVS1-397 (which is synonymous with -401) polymorphism does not influence the HDL-C response to HRT (Kjaergaard et al. 2007). Our focus is on elderly women, and we did not identify a relationship between ERα IVS1-401 and HDL-C levels, as shown in Table 5. We did, however, observe a relationship between HDL-C and the factor VII Arg353Gln polymorphism, with the GG genotype being associated with higher HDL-C levels than the AG+AA genotypes ($P=.049$). This finding was supported by comparison of the HDL-C to LDL-C ratio in each genotype in the same manner ($P=.027$). This ratio was not significant for eNOS Glu298Asp (GG; 0.63 ± 0.03, TG+TT 0.55 ± 0.07), and ERα IVS1-401 (CC; 0.51 ± 0.06, TC+TT; 0.63 ± 0.10). It is interesting to consider that such an SNP could partially impact the circulating levels of HDL-C in elderly individuals, but not in younger individuals; however, there is currently no scientific evidence to support the influence of SNPs on clinical biomarker levels that are only present in the elderly.

We have provided new evidence that the eNOS Glu298Asp polymorphism is related to triglyceride levels, with the GG genotype encoding for Glu/Glu being associated with higher triglyceride levels

than the TG+TT genotypes ($P=.031$). In addition, eNOS Glu298Asp genotype has an effect on triglyceride levels dichotomized by its demarcation line, according to the chi-square test ($P=.021$). It is possible that the high frequency of the GG genotype (86%) has masked the results of statistical analyses presented in past reports (Metzger et al. 2007). Because of the small sample study, ours has no power to analyze the differences in cardiovascular events between GG and TG+TT genotypes.

Whether eNOS Glu298Asp is a functional SNP or not continues to be widely discussed. There has been report on eNOS Glu298Asp and cardiac disease, including hypertension, showing that T allele may be involved in a higher risk (Srivastava et al. 2008). Importantly, this SNP resulting non-functional has also been reported in the yeast *Pichia pastoris* and in human endothelial cells (Golser et al. 2003; McDonald et al. 2004). Based upon the inconsistently reported functionality of this polymorphism, we suggest that further research is required to clarify the cell types in which the eNOS Glu298Asp polymorphism is functional.

In this report, the most novel finding obtained by focusing the analysis on elderly women is the relationship between the ERα IVS1-401 polymorphism and plasma BNP concentration. BNP is composed of 32 amino acids. It is synthesized in the heart ventricles, and is a well-known biomarker for heart failure (Tsutamoto et al. 1999). Neither its transcriptional regulation nor its biochemical importance is well understood (Daniels and Maisel 2007). For the ERα IVS1-401 polymorphism, the C allele, but not the T allele, is thought to result in elevated ERα expression (Herrington et al. 2002a; Schuit et al. 2004). This C allele, results either positive or negative against protective effect on cardiovascular disease (Hirschberg et al. 2009). Although estrogen up-regulates BNP mRNA and protein levels in rat neonatal cardiomyocytes (Pedram et al. 2005) and ERα and BNP proteins are both produced in adult rat cardiomyocytes (Nuedling et al. 1999; Pedram et al. 2005), there are no reports on the relation of polymorphism of ERα and BNP. Further, a previous study of ER knockout mice showed that ERβ encoded by the ESR2 gene, and not ERα, might be important for protection against heart failure (Pelzer et al. 2005; Babiker et al. 2006; Pedram et al. 2008). ERβ is known to distribute in atherosclerotic area not normal artery nor ubiquitously and the study of SNP on ERβ in human is rare. The relation of the contribution to heart failure between ERα and ERβ, especially the relation to gene polymorphism needs to be clarified.

Overall, the present results suggest that ERα IVS1-401 influences the estrogen/BNP cascade. It is remarkable that no such finding has been reported in the past, since both ERα and BNP are major factors, and produced in the same cells as discussed above. Therefore, it is possible that this study's population focus and sample collection is a key that may lead to other undiscovered SNPs that are specific to older people.

There are several guidelines for relating BNP concentration to the severity of heart failure. Interestingly, according to our results, 12 of 13 samples from ERα IVS1-401 CC genotype carriers contained under 80 pg/mL BNP (as shown in Fig. 2), which is below the limit of 100 pg/mL and outside of the gray zone of 100–500 pg/mL (Maisel et al. 2002; Brenden et al. 2006). The implication that the ERα IVS1-401 polymorphism has clinical importance on BNP levels, it needs to be further studied in larger case-control studies and in other countries, since our study size is limited and ethnic difference is untouched. We suggest that, when profiling elderly persons' clinical marker levels in order to judge their predisposition to specific diseases, SNP genotypes may play a role as prognostic factors in elderly.

Limitation of the study

This is a relatively small sample size, and a spurious association cannot be fully ruled out.

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Appendix A. Supplementary data

Supplementary data associated with this data can be found in the online version at 10.1016/j.lfs.2009.06.009.

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A hydroxymethylglutaryl coenzyme a reductase inhibitor improves endothelial function within 7 days in patients with chronic hemodialysis

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ABSTRACT

Background: Atherosclerosis-related diseases are leading causes of morbidity among patients undergoing hemodialysis. The effects of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) on the endothelial function of hemodialyzed patients are not known.
Methods and results: For 16 weeks, we prescribed simvastatin (low dose: 5 mg or moderate dose: 10 mg) to 28 patients (low dose: $n=14$, 61.2 ± 8.6 years, moderate dose: $n=14$, 60.8 ± 10.2 years) and chose 9 patients (61.5 ± 5.2 years) without prescriptions as controls. We compared the effects of statin on lipids, flow-mediated endothelium-dependent and nitroglycerin-induced endothelium-independent dilatation (%FMD, %NTD), and markers of oxidant stress and atherosclerosis. Serum HDL-cholesterol and triglycerides did not change significantly in any of the three groups; however, LDL-cholesterol was decreased at 16 weeks in both simvastatin groups. The %FMD and plasma NOx increased at 1 and 16 weeks in both statin groups, but not in the control group ($P<0.01$). The %NTD did not change. Oxidized LDL, VCAM-1, and 8-isoprostane decreased significantly after 16 weeks in both statin groups; however, TNF-α and interleukin 6 did not change. In the control group, no significant changes in these parameters were observed. Multiple regression analyses showed that the (short) period of hemodialysis and (young) age are significant factors associated with %FMD improvement.
Conclusions: A statin improved impaired endothelial function in the arteries of chronic dialysis patients, in part by enhancing NO bioavailability within one week. Improved endothelial function is in line with the anti-atherosclerotic effects observed in patients undergoing chronic hemodialysis.

1. Introduction

Atherosclerosis-related diseases such as myocardial infarction and ischemic heart disease-related heart failure are the leading causes of morbidity among patients undergoing hemodialysis in developed countries, such as the United States or Japan [1]. It is well known that lipid-lowering therapy, especially the use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), decreases the risk of coronary events in both primary and secondary prevention [2,3]. The anti-atherosclerotic effects of statins are thought to be attributable to changes in plasma lipid levels (i.e., decreased LDL cholesterol and increased HDL cholesterol) [2,3]. We have reported that treatment of diabetic patients with a statin resulted in improved endothelial function before the appearance of its effects on lipids, in other words, in three days [4]. Statins are known to up-regulate endothelial nitric oxide synthase (eNOS) in cultured endothelium and in the endothelium of the aorta of rabbits fed a high-cholesterol diet [5,6]. The direct action of statins on the atherosclerotic arteries of rabbits, without lowering plasma lipids, has also been studied [6]. However, to our knowledge, there are no existing studies on this direct action in atherosclerotic arteries of patients undergoing hemodialysis. The present study focuses on the effect of statins on endothelial function, especially flow-mediated dilatation and nitric oxide (NO)-related endothelial function in hemodialytic atherosclerotic arteries of humans. We selected simvastatin, which is thought to have a long and strong tissue affinity [7]. Because we anticipated difficulty in improving endothelial function in patients undergoing hemodialysis, we examined two treatment groups, one of which received a low dose (5 mg/day, the usual dose in Japan) and the other a moderate dose of simvastatin (10 mg/day).

2. Materials and methods

2.1. Patients

Endothelial function was assessed in 37 hemodialysis patients (aged 60.6 ± 9.2 years, 17 males, and 20 females) with or without mild hyperlipidemia (LDL cholesterol, 95.9 ± 37.1 mg/dl, 72.9 to 172.8 mg/dl). The participants were ambulatory and were patients at our medical clinics (Souen Chuo Hospital, Sapporo, Japan; Nakashibetsu Public Hospital, Nakashibetsu, Japan; and Kyouritsu Hospital, Nagoya, Japan). They had not been prescribed

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Table 1
Biochemical profile, *$P<0.05$ between low and moderate dose of statin.

	Statin (low dose)	Statin (moderate dose)	Control
Male/female (number)	6/8	6/8	4/5
Age (y.o.)	61.2 (8.6)	60.8 (10.2)	61.5 (5.2)
BMI	24.9 (2.7)	24.7 (2.8)	25.0 (2.0)
Period of H.D. (months)	**32.4 (14.1)**	**64* (44.2)**	**51 (28.5)**
Origin of H.D. (%)			
Diabetes mellitus	57.1	43.0	55.5
Glomerulonephritis	21.5	21.5	22.2
Hypertension	**0**	**7.1***	**0**
Others	14.3	28.6	22.2
Complication (%)			
Ischemic heart disease	28.7	28.7	22.2
Hypertension	64.3	64.3	55.5
Diabetes mellitus	64.3	43.0	44.4
Smoking	21.5	14.3	22.2
Medication affecting endothelial functions (%)			
ACEis/ARBs	28.7	28.7	33.3
Other anti-hypertensive drugs	50.0	57.1	55.5
diuretics	21.5	21.5	22.2
nitrates	0	0	0
Anti-platelet/anti-coagulant	0	0	0
Plasma lipids			
Total chol. (mg/dl)	135.5 (36.0)	176.1 (46.1)	149.4 (44.4)
Triglyceride (mg/dl)	99.8 (57.4)	133.8 (62.0)	106.3 (40.1)
LDL chol. (mg/dl)	**83.2 (34.3)**	**118.0* (33.8)**	**91.1 (30.2)**
HDL chol. (mg/dl)	32.4 (11.7)	32.1 (6.2)	33.4 (7.8)
Cytokines and others			
sVCAM-1 (ng/ml mg prot,)	880.2 (168.2)	1000.4 (151.9)	919.2 (139.0)
TNFα (pg/ml)	**5.0 (1.9)**	**9.8* (5.4)**	**6.3 (3.2)**
IL-6 (pg/ml)	7.9 (3.3)	3.6 (1.4)	6.3 (2.6)
8epi ISP (ng mg protein/ml)	21.4 (6.4)	40.1(6.8)	29.1 (5.7)
Oxidized LDL (mg/ml)	24.3 (33.5)	29.4 (34.6)	27.0 (42.4)
Vascular and NO related profile			
Baseline diameter (mm)	3.01 (0.18)	2.94 (0.19)	2.95 (0.22)
Peak diameter (mm)	3.17 (0.25)	3.09 (0.25)	3.10 (0.24)
%FMD	5.6 (1.0)	4.8 (0.9)	5.2 (0.9)
GTN-induced peak diameter (mm)	3.31 (0.19)	3.24 (0.21)	3.26 (0.20)
%NTG-D	10.9 (1.1)	10.0 (0.9)	10.2 (0.9)
NOx (μM)	129.2 (16.8)	111.6 (18.1)	120.4 (15.1)

Bold emphasis and * show the significant differences between moderate dose of statin group and other two (low dose and control) groups.
The numbers are the mean ± SD, or the percent of each groups. *$P<0.05$ vs. data in low dose of statin treatment.
Abbreviations: Statin (low dose): simvastatin 5 mg/day group, statin (moderate dose): simvastatin 10 mg/day group. control: no prescription group.
BMI:Body Mass Index, H.D.:hemodialysis, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, LDL: low-density lipoprotein, HDL: high-density lipoprotein, chol.:cholesterol, 8epi ISP: 8epiisoprostan, FMD: flow-mediated dilation, NTG-D: nitroglycerin-mediated dilation.

lipid-lowering drugs for at least 6 weeks prior to the study. None had suffered acute coronary events for at least three months prior to the study. Based on the plasma LDL levels of the patients, they were randomly assigned to treatment in the low-dose simvastatin group or the control group (baseline LDL< 100 mg/dl: 5 mg/d of simvastatin; $n = 14$, 6 men, LDL 82.3 ± 34.3 mg/dl and no prescription; $n = 9$, 4 men, LDL 91.1 ± 30.2 mg/dl) or to the moderate-dose simvastatin group (10 mg/day; $n = 14$, 6 men, baseline LDL< 100 mg/dl, LDL 118.0 ± 33.8 mg/dl). Prescription treatment lasted 16 weeks. All patients provided informed consent, agreed to the protocols, and were willing to participate in the study. Ineligible patients included those who had not taken any estrogen for >12 weeks. The study was approved by the ethics committee of Nagoya University Graduate School of Medicine. The participants had received hemodialysis for 4.1 ± 1.2 years, their average systolic and diastolic blood pressure was 127.4 ± 11.7/78.2 ± 9.8 mm Hg, and their complicated diseases included ischemic heart disease, hypertension, and diabetes mellitus (Table 1). Seven patients were smokers (Table 1). Their use of medications that can affect endothelial function, such as angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs), other antihypertensive agents, and diuretics, is indicated in Table 1. Diabetic nephropathy was most frequent underlying renal disease. The patient profiles, including other backgrounds, are shown in Table 1. Patients in the moderate-dose group had received hemodialysis for a longer term, on average, and most of them suffered from hypertension. Between the low and moderate-dose groups and the controls, there were no significant differences among other parameters, including prescribed agents.

2.2. Vascular function

Flow-mediated dilatation (FMD) and dilatation by nitroglycerin were determined according to a method described previously [8]. Briefly, the diameter of the right brachial artery was measured by a high-resolution ultrasound cardiograph (SONOS 2000, Hewlett Packard). Blood pressure was monitored every 2 min. To produce reactive hyperemia, blood flow to the forearm was prevented by inflation of the cuff on the arm to 250 mm Hg for 5 min. The diameter was measured from the anterior to the posterior interface between the media and adventitia and was calculated from 3 cardiac cycles synchronized with the R-wave peaks on the ECG. The measurement obtained at 60 s after cuff release showed maximal dilatation. The diameter change was expressed as the percent change relative to the diameter during the initial resting scan (%FMD). Fifteen minutes later, a resting scan was recorded and a sublingual nitroglycerin spray (300 μg, Toa Eiyou Co.) was administered. Three minutes later, the last scan was performed. The diameter change was expressed as the percent dilatation by nitroglycerin (%NTD). In our study, the interobserver variability for repeated measurements of resting arterial diameter was 0.05 ± 0.02 mm. The intraobserver variability for repeated measurements of resting arterial diameter was 0.02 ± 0.02 mm. In other words, the reproducibility (<0.1% difference) of the %FMD was greater than 96.3%. Vascular function was studied before commencing treatment, and then after 1 week and 16 weeks of treatment; it was studied in the morning of the day of hemodialysis, and it was performed just before hemodialysis during overnight fast status.

2.3. Blood sampling

Blood sampling was performed on the morning of the ultrasound examination (day of hemodialysis) under overnight fast status. Serum total cholesterol, triglyceride, and HDL cholesterol concentrations were measured [9]. Plasma nitrite and nitrate levels ($NO2^-$ and $NO3^-$) were measured with an automated NO detector/high-performance liquid chromatography system (ENO10, Eicom Co., Kyoto, Japan), as previously reported [10]. In brief, nitrite and nitrate levels in the patient's plasma were separated by a reverse-phase separation column, and nitrate was reduced to nitrite in a reduction column. Nitrite was mixed with a Griess reagent, and the absorbance at 540 nm was measured by a flow-through spectrophotometer. The concentration of interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), soluble vascular cell adhesion molecule 1 (sVCAM-1), and 8-isoprostane (8-epi-prostaglandin F2) were assessed by ELISA kits (Cytoscreen Immunoassay Kit, Bioxytech 8-isoprostane assay kit, Oxis International, Inc). Plasma Ox-LDL was assayed using a Kyowa Medex MX kit (Kyowa Medex, Inc., Tokyo), which is a sandwich-type enzyme immunoassay using anti-oxidized phosphatidylcholine monoclonal antibody (DLH3) and anti-human apolipoprotein-B antibody [11,12].

2.4. Safety measures

All adverse events were recorded at each examination. Physical examinations, hematology, and serum chemistry assays (liver and renal function and creatine phosphokinase) were conducted throughout the study.

2.5. Statistical analyses

Data are presented as the mean ± SD of each group of patients. $P<0.05$ was considered to indicate statistical significance in all analyses. All statistical analyses were performed using JMP software (version 6, SAS Institute Inc., Cary, NC). Differences between categorical baseline characteristics were tested by the chi-square test. In addition, the parameters of interest were tested for statistical difference by ANOVA between the three different groups (low dose, moderate dose, and control groups).

Multivariate logistic regression analyses were done with adjustment for baseline characteristics such as sex.

3. Results

Table 1 shows the baseline profiles for each group. The period of hemodialysis, LDL cholesterol, and TNF-α were different between subjects receiving low (5 mg/day) doses of simvastatin or subjects in the control group and subjects receiving moderate (10 mg/day) doses of simvastatin (Table 1). No other differences were observed in the values for each condition shown in Table 1. Serum lipid concentrations (total cholesterol, triglycerides, and HDL cholesterol) remained unchanged in all patients in response to 1 week of treatment with simvastatin, and LDL cholesterol was decreased at 16 weeks in both statin groups (Table 2). The sVCAM-1 level decreased significantly at 1 week in both statin treatment groups (especially in the low-dose group), but not in the control group (Table 2). However, TNF-α and IL-6 did not change during the course of the experiment (Table 2). No abnormal data were noted in

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Table 2
Change of lipids and cyotokine concentrations by statin treatment.

Statin treatment	Low dose (5 mg/day)			Moderate dose (10 mg/day)			Control		
	Before	1 wk	16 wks	Before	1 wk	16 wks	Before	1 wk	16 wks
Total chol. (mg/dl)	135.5 ± 36.0	122.1 ± 46.3	120.3 ± 41.4	171.1 ± 46.1	151.0 ± 45.4	**128.2* ± 23.1**	149.4 ± 42.4	153.1 ± 49.1	152.5 ± 48.5
Triglycerides (mg/dl)	99.8 ± 57.4	95.2 ± 52.5	101.4 ± 48.5	133.8 ± 62.0	116.7 ± 55.7	103.0 ± 44.1	108.3 ± 40.6	113.2 ± 52.1	115.0 ± 54.3
HDL chol. (mg/dl)	32.4 ± 11.7	34.2 ± 12.8	35.3 ± 13.6	32.1 ± 6.2	31.8 ± 7.1	35.8 ± 9.4	33.1 ± 7.9	32.9 ± 7.2	33.6 ± 9.0
LDL chol. (mg/dl)	83.2 ± 34.3	71.1 ± 33.0	**64.7* ± 28.3**	109.6 ± 33.8	89.0 ± 33.7	**74.5* ± 30.6**	93.5 ± 31.2	94.1 ± 35.3	95.0 ± 32.8
sVCAM-1 (ng/ml mg protein)	880.2 ± 168.2	**686.2* ± 132.1**	**619.2* ± 210.4**	1027.4 ± 151.9	798.8 ± 115.4	**765.6* ± 115.1**	922.6 ± 137.2	938.2 ± 166.0	940.1 ± 169.1
TNFα (pg/ml)	5.0 ± 1.9	5.3 ± 2.3	4.5 ± 1.1	9.1 ± 5.4	9.0 ± 5.4	8.9 ± 3.1	6.6 ± 3.4	6.4 ± 3.7	6.4 ± 3.1
IL-6 (pg/ml)	7.9 ± 3.3	7.7 ± 2.5	7.9 ± 2.3	4.6 ± 1.4	4.9 ± 2.1	5.6 ± 2.0	6.5 ± 2.6	6.6 ± 2.5	6.4 ± 2.8

Bold emphasis and * show the significant differences vs. value in before treatment.
Low dose(5 mg/day): simvastatin 5 mg/day group, moderate dose(10 mg/day): simvastatin 10 mg/day group. Control: no prescription group. The numbers are the mean ± SD.
*$P<0.05$ vs. the value in before treatment. Abbreviations: low dose (5 mg/day): simvastatin 5 mg/day group, moderate dose/ 10 mg/day): simvastatin 10 mg/day group. Control: no prescription group.
LDL: low-density lipoprotein, HDL: high-density lipoprotein, chol.:cholesterol.
Before: before treatment, 1 wk; treatment with simvastatin for 1 week, 16 wks; treatment with simvastatin for 16 weeks.

the other biochemical measures, including creatine phosphokinase levels, throughout the treatment term in either group (data not shown).

The endothelium-dependent flow-mediated dilatation (%FMD) in those receiving simvastatin significantly increased at 1 week in both statin groups (low dose: 5.7% to 8.7% in 1 week, $P<0.01$, and 10.1% in 16 weeks, $P<0.001$, moderate dose: 4.5% to 5.7% in 1 week, $P<0.01$, and 7.9% in 16 weeks, $P<0.001$Fig. 1A). No difference in the response to nitroglycerin (%NTG) was demonstrated after 16 weeks of treatment (Fig. 1B). The %FMD after 16 weeks of treatment in both simvastatin groups tended to be higher than in patients in both groups at week 1 (Fig. 1A). In the control group, no changes were observed in %FMD or % NTG. There was no significant relationship between the degree of LDL lowering and improved endothelial function; this may suggest a direct effect of statin other than its lipid-lowering effect. However, the basal conditions, such as plasma LDL cholesterol and the period of hemodialysis, were different between the low and moderate statin groups (Table 1), and direct comparison between these two groups was difficult. The plasma nitrite/nitrate (NOx) levels also tended to become higher in patients receiving simvastatin (Fig. 2A), and low-dose simvastatin administration also caused an increase in NOx (mM) (120.4 ± 15.6 in 0 week, 77. 2 ± 5.2 in 1 week, 159.4 ± 7.61 in 16 weeks) ($P<0.05$). The 8-Epi-isoprostan (ng mg protein/ml)was decreased at 1 and 16 weeks in both statin treatment groups (low dose: 21.4 ± 6.4 in 0 week, 13. 2 ± 2.6 in 1 week, 10.1 ± 2.4 in 16 weeks), but it did not change in the control group (Fig. 2B). Oxidized LDL (mg/ml) was also decreased at 16 weeks in both statin groups (low dose: 245 ± 33.4 in 0 week, 220. 2 ± 19.2 in 1 week, 163.4 ± 17.6 in 16 weeks) ($P<0.05$ in data of 0 weeks or that of 8 weeks vs. that of 16 weeks) (Fig. 2C). However, oxidized LDL did not remain significantly lower after statin treatment when corrected for LDL cholesterol levels, and it is not evident whether a decrease in oxidized LDL or in LDL affects %FMD more. Considering dose differences with regard to the effect of statin treatment, no additional effect of a high dose of statin was observed in the levels of %FMD, NOx, sVCAM-1, 8-isoprostane, TNF-α, or IL-6. The effect of statin therapy on %FMD, NOx, and 8-epi-isoprostane tended to be greater in the low-dose group compared to the moderate-dose group without reaching the significance threshold. Since the effect of statin therapy on plasma cholesterol in this group was less pronounced, these data might favor a direct mechanism of statin therapy.

As the improvement of % FMD did not depend on (change of) LDL levels, we did multiple regression analyses inserting data in 0 weeks found to be significantly different between low dose and moderate dose

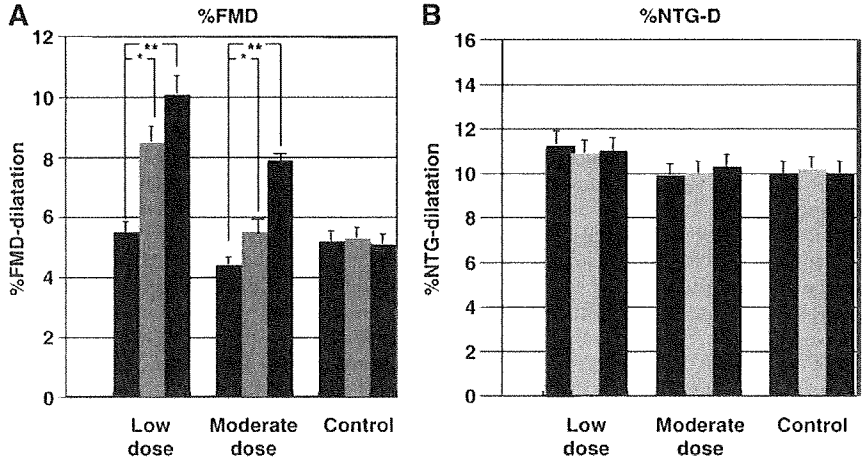

Fig. 1. A, Endothelial function assessed by measuring dilatation of the brachial artery using high-resolution vascular ultrasound in response to reactive hyperemia (FMD: endothelial-dependent flow mediated dilatation). The percent increase in vessel diameter induced by FMD (%FMD) is shown. *$P<0.05$. B, Endothelial-independent function assessed by measuring dilatation in response to sublingual nitroglycerin (NTG) infusion. The percent increase in diameter induced by nitroglycerin is shown (%NTG-D). No significant differences were observed following simvastatin treatment compared to before treatment. Data are expressed as the mean ± SD. Low dose: simvastatin 5 mg/day group, moderate dose: simvastatin 10 mg/day group. Control: no prescription group. The explanation of each bar graph in the group. Left; before treatment, middle; treatment with simvastatin for 1 week, and right; treatment with simvastatin for 16 weeks.

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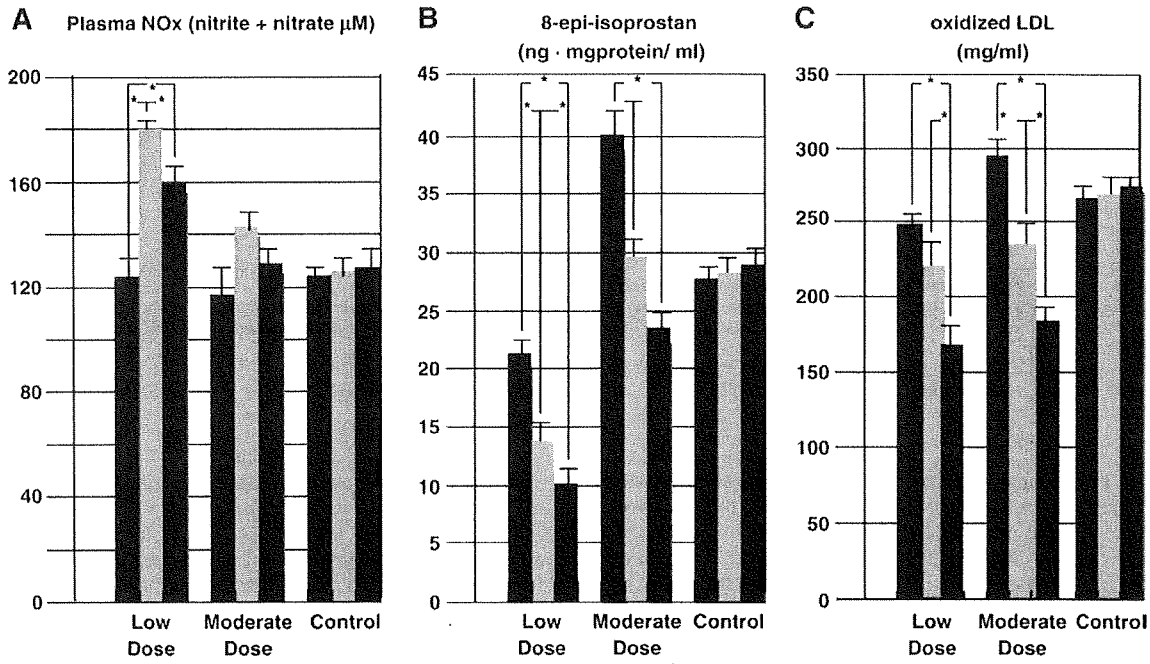

Fig. 2. Plasma concentration of nitrite/nitrate (NOx; A), isoprostane (B) or oxidized LDL (C) before and after simvastatin treatment or in the control group. Data are expressed as the mean ± SD. *$P<0.05$. Low dose: simvastatin 5 mg/day group, moderate dose: simvastatin 10 mg/day group. Control: no prescription group. The explanation of each bar graph in the group. Left; before treatment, middle; treatment with simvastatin for 1 week, and right; treatment with simvastatin for 16 weeks.

groups. We found the (short) period of hemodialysis and (young) age are significant factors associated with %FMD improvement.

4. Discussion

The guidelines of the Japan Atherosclerosis Society (2007) and NCEP (2006) state that LDL should be below 120–130 mg/dl and HDL should be greater than 40 mg/dl [13,14] in individuals with end-stage renal disease. We tried to investigate the additional effect of statin on a further decrease in LDL and other effects in patients undergoing hemodialysis. Simvastatin improved the impaired endothelial function of dialysis patients by decreasing oxidized LDL, improving the lipid profile and, at least in part, enhancing NO bioavailability.

Various mechanisms other than lipid lowering have been proposed to account for the anti-atherosclerotic effects of statins, including antioxidant activity and enhanced NO activity, as direct effects of statins on cells comprising the vascular wall [4–6,10]. Statins increase eNOS activity both *in vitro* and *in vivo* [5,6,15]. Because NO has many anti-atherosclerotic effects, such as inhibition of monocyte migration, the increased activity of eNOS in response to statins may partially explain its anti-atherosclerotic effects.

The %FMD has been studied extensively in recent years, and it is believed to reflect NO function in vessels [16]. Impairment of %FMD has been reported to precede coronary artery disease, and the %FMD is known to be low in atherosclerotic arteries [17]. Atherosclerosis is very severe in hemodialytic patients, regardless of their original diseases [18]. We noted that the %FMD in the patients evaluated in our study was low. The improvement in %FMD in hemodialysis patients through short-term statin treatment may be due to improved microvascular circumstances or blood fluidity rather than improvement in the atherosclerotic conduit vessel itself [19,20]. The fact that statistical analyses show that the period after introducing hemodialysis is a significant determinant may support this concept.

There are few reports on the effects of statin in patients undergoing hemodialysis [21–25]. Although the number of cardiac events may be reduced, total cardiovascular events, mortality, and total mortality were reported to be the same with or without statin [21–23]. In the present study, statin treatment does not seem to increase HDL cholesterol or reduce plasma triglycerides. Although this may be due to the specific composition of the study population under hemodialysis, it may remain a noteworthy observation and may be related to the effect of statin as mentioned above. Six weeks of atorvastatin treatment (40 mg/day) was reported to improve small artery compliance, but not FMD, in patients in stages 3–5 stages of CKD and hemodialysis [24], although the number of hemodialysis patients was small and a more detailed analysis may be necessary. Furthermore, five months of treatment with pravastatin in patients with chronic dialysis did not have a significant effect on surrogate markers of endothelial function, such as IL-6, sVCAM-1, sICAM-1, etc. Although the CKD and hemodialysis study [25] did not measure NO-related products and we cannot compare the data directly, the kind of statin and the condition of patients with dialysis, such as the period of dialysis, might account for the discrepancy. The difference in the present study's data with regard to the grade of FMD improvement between low and moderate-dose groups may support this explanation.

However, there is no information on the effect of the period of hemodialysis and endothelial function on the previous study's results [26]. Renal failure with or without hypercholesterolemia might further worsen endothelial function because of the presence of asymmetric dimethylarginine and/or uremic toxin [26]. Inhibition of arginine synthesis by urea is a mechanism of arginine deficiency in renal failure that leads to increased hydroxyl radical generation. However, the effect of uremic toxin should be decreased by hemodialysis. Endothelial function, as measured by %FMD, improved in the hemodialytic patients receiving simvastatin after only seven days, and the same trend was observed for plasma nitrite/nitrate, supporting the hypothesis that simvastatin improves endothelial NO function itself. This is the first report that an improvement in %FMD was observed in patients receiving hemodialysis.

In a thrombogenic event such as myocardial infarction, the thrombosis occurs due to impaired endothelial function and atherosclerosis caused by activation of cytokines or adhesion molecules such as VCAM-1 [26,27]. In the present study, VCAM-1, oxidized LDL, and isoprostane were decreased by statin. Improved endothelial function,

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such as increased %FMD, decreased adhesion molecules, and decreased free radicals may prevent vascular thrombogenic events [27–29]. When statins improve %FMD levels via a direct effect, an improvement in atherogenic molecules and free radicals as well as lipid lowering should result in further improvement of endothelial function. Although we reported improved %FMD in as short a time as three days [4], a short-term effect of statin independent of plasma lipid levels, the possibility of a pleiotropic effect without any relation to plasma lipid is interesting. Taken together, the detailed mechanism of the improvement in %FMD might be different between what has been previously reported for diabetics and what we determined in the present study for hemodialytic patients. In the present study, %FMD levels were greater after 16 weeks than after 7 days of treatment. The continuous improvement in %FMD levels after statin treatment for 16 weeks may mean that both mechanisms (direct and indirect effects) contribute to this action [5,6,30–32]. The data for 8-isoprostan, a marker of reactive oxygen species, support this hypothesis. Consequently, the bioavailability of simvastatin in vessel walls is increased and the direct effect may more easily occur.

The period of hemodialysis and the TNF-α level might constitute the difference in background between study participants receiving low or moderate doses of statin. Since LDL levels in each group became the same after treatment and TNF-α levels did not change after statin treatment in the present study, it is possible that the term of hemodialysis may reflect the severity of atherosclerosis. These differences may mask the different effects of different doses of statin, although the mechanism requires further clarification.

In the present study, 8-isoprostane, an oxidant marker, was also decreased after 16 weeks. In atherosclerotic arteries, the increase in oxygen radicals and their decrease in response to statin treatment are well known. Statins could decrease $O2^-$ release from rabbit aortas when rabbits were fed regular chow [33,34]. It is possible that an increase in NO down-regulates an $O2^-$ releasing enzyme, such as NADPH oxidase [35–37]. A decrease in the levels of $O2^-$ releasing enzyme may contribute to a prolonged NO lifespan and indirectly improve endothelial function [37,38].

Our data may partially support simvastatin's anti-atherosclerotic effects, especially with regard to restoration of endothelial function, which may relate to the stabilization of atheroma. There is a common ground between the changes in levels of adhesion molecules and endothelial function resulting from statin treatment in this study and the anti-atherosclerotic effect of the statin.

5. Limitations of the study

There were a limited number of patients in the present study. The slight tendency toward lipid profile changes was observed even seven days after treatment, but this may have been inevitable because the hemodialysis was performed three times per week and the conditions used to measure %FMD and %NTG may need to be adjusted. These effects are not guaranteed to continue for years. Recently, atorvastatin was reported to have no beneficial effect during the end stage of renal failure, and the merit of statin may be limited only to the arteries of patients during the early term of chronic hemodialysis without severe atherosclerosis. However, there were many differences in conditions in the pertinent study, such as the amount prescribed or the frequency of adverse effects. Further examination of whether these effects persist is needed.

In conclusion, in elderly patients undergoing hemodialysis, seven days of treatment with simvastatin may improve endothelial function of atherosclerotic arteries. Changes such as those observed in %FMD and adhesion molecules induced by simvastatin could prevent A–V shunt trouble or cardiovascular diseases due to thrombotic occlusion in patients with chronic hemodialysis.

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Low HDL Cholesterol Is Associated With the Risk of Stroke in Elderly Diabetic Individuals

Changes in the risk for atherosclerotic diseases at various ages

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OBJECTIVE — To clarify the relationship between lipid levels and ischemic heart disease (IHD) and cerebrovascular disease (CVD) in diabetic individuals.

RESEARCH DESIGN AND METHODS — The Japan Cholesterol and Diabetes Mellitus Study is a prospective cohort study of 4,014 type 2 diabetic patients (1,936 women; mean ± SD age 67.4 ± 9.5 years). Lipid and glucose levels and other factors were investigated in relation to occurrence of IHD or CVD.

RESULTS — IHD and CVD occurred in 1.59 and 1.43% of participants, respectively, over a 2-year period. The relation of lower HDL or higher LDL cholesterol to occurrence of IHD in subjects <65 years old was significant. Lower HDL cholesterol was also significantly related to CVD in subjects ≥65 years old and especially in those >75 years old (n = 1,016; odds ratio 0.511 [95% CI 0.239–0.918]; $P < 0.05$). Stepwise multiple regression analysis with onset of CVD as a dependent variable showed the same result.

CONCLUSIONS — Lower HDL cholesterol is an important risk factor for not only IHD but also CVD, especially in diabetic elderly individuals.

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Type 2 diabetes, dyslipidemia, and aging are independent risk factors for cardiovascular diseases. Japanese individuals have lower rates of ischemic heart disease (IHD) and higher rates of cerebrovascular disease (CVD); however, diabetic individuals have an increased risk of IHD (1,2). Risk factors for IHD or CVD in elderly diabetic individuals are not fully known (3), and the Japan Cholesterol and Diabetes Mellitus Study was formulated to evaluate them (Umin Clinical Trials Registry, clinical trial reg. no. UMIN00000516; http://www.umin.ac.jp/ctr/index.htm).

RESEARCH DESIGN AND METHODS

— The Japan Cholesterol and Diabetes Mellitus Study is a single-center prospective cohort study comprised of 4,014 Japanese diabetic individuals on a consecutive outpatient basis recruited between September 2004 and March 2005 (1,936 women; mean ± SD age 67.4 ± 9.5 years [range 35–83 years]). Patients with previous IHD (myocardial infarction, unstable angina pectoris, angioplasty, or bypass grafting) or CVD (stroke) were excluded. Follow-up information was available for 98.2 and 92.3% of patients enrolled in the first and second years, respectively. Patients were divided into those aged <65 years, 65–74 years, and >75 years (n = 1,267, 1,731, and 1,016, respectively). The primary end points were onset of IHD or CVD. Plasma lipid, glucose, A1C, and other relevant levels were measured annually.

The study was approved by institutional review boards and by the safety-monitoring board. All events were confirmed by the organizing committee annually. The guidelines of the Japan Atherosclerosis Society (2002), stating that LDL cholesterol should be <120 mg/dl and HDL cholesterol >40 mg/dl in diabetic individuals, and the American Diabetes Association criteria for diagnosis of type 2 diabetes were used (4,5).

Results are presented as means ± SD. All statistical analyses were performed using JMP software (SAS Institute, Cary, NC). Incidences were analyzed in relation to risk factors. Univariate and multiple logistic regression analysis and stepwise analysis were used. Values of $P < 0.05$ were considered significant.

RESULTS

— Mean A1C, fasting plasma glucose, LDL cholesterol, triglyceride, HDL cholesterol, and systolic and diastolic blood pressure levels on registration were 7.53 ± 1.12%, 159.4 ± 52.7

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Table 1—*Adjusted multiple regression analyses of factors found to be significant by univariate regression analysis for IHD or CVD, as well as major atherogenic risk factors; total* n = *4,014*

	<65 years old (*n* = 1,276)		65–74 years old (*n* = 1,731)		≤75 years old (*n* = 1,016)	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
IHD						
Sex	1.469 (1.02–1.94)	0.02*	1.109 (1.02–1.74)	0.04*	0.829 (0.23–3.06)	0.78
Age	1.063 (0.96–1.20)	0.28	0.991 (0.86–1.15)	0.99	0.996 (0.83–1.17)	0.87
LDL cholesterol	1.225 (1.02–2.04)	0.04*	1.001 (0.72–1.25)	0.89	0.776 (0.43–1.40)	0.40
HDL cholesterol	0.659 (0.39–0.98)	0.04*	0.939 (0.68–1.25)	0.38	0.946 (0.58–1.29)	0.23
Triglycerides	1.356 (1.00–2.02)	0.05	0.731 (0.52–1.94)	0.18	0.881 (0.46–1.70)	0.71
A1C	1.179 (0.75–1.88)	0.27	1.082 (0.76–1.55)	0.67	1.274 (0.57–2.35)	0.44
SBP	0.702 (0.49–1.09)	0.15	1.082 (0.79–1.69)	0.15	1.051 (0.58–1.89)	0.87
DBP	1.020 (0.97–1.05)	0.28	1.088 (0.73–1.27)	0.24	1.998 (0.99–4.35)	0.08
CVD						
Sex	1.158 (0.68–2.17)	0.47	1.004 (0.79–1.69)	0.82	0.847 (0.45–1.52)	0.58
Age	1.006 (0.94–1.10)	0.88	0.982 (0.82–1.14)	0.39	1.139 (0.99–1.30)	0.06
LDL cholesterol	1.099 (0.98–1.23)	0.06	1.067 (0.76–1.44)	0.51	1.128 (0.64–1.59)	0.71
HDL cholesterol	0.888 (0.64–1.48)	0.09	0.758 (0.53–0.98)	0.04*	0.511 (0.24–0.92)	0.04*
Triglycerides	1.147 (0.68–2.04)	0.62	1.070 (0.69–1.67)	0.75	1.355 (0.75–2.56)	0.32
A1C	0.996 (0.64–1.28)	0.52	1.019 (0.75–1.74)	0.54	1.015 (0.60–1.72)	0.95
SBP	1.005 (0.67–1.33)	0.86	0.991 (0.94–1.13)	0.35	1.063 (0.62–1.57)	0.75
DBP	1.109 (0.61–2.13)	0.74	1.303 (0.81–2.09)	0.27	1.045 (0.68–1.5)	0.59

	IHD				CVD			
	<65 years old	65–74 years old	≤75 years old	Total	<65 years old	65–74 years old	≤75 years old	Total
HDL cholesterol (mg/dl)								
<44	2.31	2.49	1.68	2.14	1.13	1.99	2.62*	2.01
44–53	1.45	1.45	1.64	1.50	1.05	1.84	2.15*	1.64
54–63	1.25	1.41	0.98	1.23	1.44	0.80	0.88*	1.04
≥64	0.42	1.69	0.99	1.19	1.0	0.80	0.45*	0.72

Data were adjusted for sex. The ratio of male to female subjects is 1.1. *Statistically significant ($P < 0.05$). DBP, diastolic blood pressure; SBP, systolic blood pressure.

mg/dl, 120.3 ± 32 mg/dl, 140.6 ± 108.3 mg/dl, 55.8 ± 18.0 mg/dl, 136.5 ± 17.1 mmHg, and 75.1 ± 11.1 mmHg, respectively. Insulin and oral agents for diabetes were prescribed for 19.9 and 70.5% of individuals, respectively. Dyslipidemia was seen in 79.1%, and antihyperlipidemic drugs were prescribed in 59.0%. Mean lipid and glucose metabolism levels did not change significantly over the 2-year study period.

In the first and second years, 83 and 69 vascular events occurred, respectively. IHD and CVD occurred in 0.80 and 0.71% of total patients per year. The relationship between IHD or CVD and background factors such as LDL cholesterol levels in each age-group was analyzed by univariate logistic regression.

Sex, age, LDL cholesterol, HDL cholesterol, and triglyceride were significantly related to IDH in patients aged <65 years. Age, sex, history of hypertension, and antihypertensive drugs were related in patients aged between 65 and 74 years, and sex and systolic and diastolic blood pressure were related in patients aged > 75 years. CVD and LDL cholesterol were related in patients aged <65 years, and HDL cholesterol and systolic blood pressure were related in patients aged >75 years.

We performed multiple regression analysis with factors found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors (A1C, etc.) in three age-groups (Table 1). LDL and HDL cholesterol were associated with IHD in patients aged < 65 years but not in other age-groups. Sex was associated with IHD in individuals aged <74 years. HDL cholesterol was also associated with CVD in individuals between aged between 65 and 74 years and >75 years.

Stepwise multiple regression analysis was performed using factors that were found to be significant by univariate regression analysis for IHD or CVD and other atherogenic risk–related factors. HDL and LDL cholesterol were associated with IHD in individuals aged <65 years (HDL cholesterol odds ratio 0.79 [95% CI 0.58–0.96; $P = 0.04$] and LDL cholesterol 0.60 [0.33–0.99; $P = 0.04$]). HDL cholesterol was associated with CVD in individuals aged between 65 and 74 years and ≥75 years (65–74 years 0.73 [0.56–0.94; $P = 0.04$] and ≥75 years 0.60 [0.35–0.91; $P = 0.01$]).

The relation of age or HDL cholesterol to IHD and CVD was evaluated in quartile categories. HDL cholesterol levels were inversely correlated with IHD in individuals aged <65 years (hazards ratio 0.633 [95% CI 0.428–0.975]) but not in other groups. The relationship between CVD and HDL cholesterol was prominent in those aged >75years but not in other age-groups (Table 1). There were no sex-related differences in the relationship of HDL cholesterol with CVD. There was no relationship between LDL, triglyceride, fasting blood glucose, or A1C and the frequency of CVD.

CONCLUSIONS — This study represents one of the largest-scale attempts to examine IHD and CVD in middle-aged and elderly diabetic individuals. In the U.S., evidence suggests that middle-aged diabetic individuals have an IHD risk similar to that for individuals with myocardial infarction (6). However, this risk may not exist in elderly diabetic individuals. Many guidelines to prevent atherothrombotic diseases recommend strict control of LDL cholesterol in diabetic patients but the same guideline for HDL cholesterol control (40 mg/dl) as that used for nondiabetic subjects (4–7).

A novel finding was that type 2 diabetic elderly individuals had frequent CVD, and incidence rates were associated with HDL cholesterol. Few data were available for the relationship among elderly, type 2 diabetes, and CVD (8,9).

There have been three large-scale clinical studies of statins that included participants aged up to 75 years (10–12). Although they reported that statins exerted effects on IHD (including in diabetic individuals), effects were not pronounced. (Prosper reported that statins induced a 16% decrease in IHD without any effects on CVD.) The data suggest that because LDL cholesterol decreased, simple LDL cholesterol control may not prevent IHD or CVD in elderly individuals. Our study shows the importance of HDL cholesterol in CVD in elderly diabetic individuals and in IHD in middle-aged diabetic individuals. If HDL cholesterol is well controlled in elderly diabetic patients, then CVD and IHD might be decreased to the levels found in middle-aged cohorts. Patients prescribed statins whose HDL cholesterol was <40 mg/dl showed the same risk (data not shown). Although medicated patients may be more conscious of diseases, HDL cholesterol is a strong risk factor and masks the effects of statins.

In conclusion, HDL and LDL cholesterol were risk factors for IHD in diabetic patients aged <65 years. In addition, HDL cholesterol was a risk factor for CVD in elderly diabetic subjects, especially those aged >75 years. HDL cholesterol may help prevent CVD in elderly diabetic subjects. Risk factors for IHD and CVD appear to change with advancing age.

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次々と発表される大規模臨床試験の結果をいかに読み取り、自らの診療に活かす？

順天堂大学大学院・(文科省事業)スポートロジーセンター 河盛隆造

最前線の多くの医師は、次々と発表される大規模臨床試験の結果をどのように評価し、自らの日々の診療に活用しておられるのであろうか？「患者さんの病態は一例一例異なる、かつ治療に反応して刻々と変動している。その時点での病態にあった治療薬を選択し用いているのが実情だ。数千人の患者を1例とみなして、同一の治療を永年施した結果を提示されたとしても、自らの診療が一気に変わるとは思えない」という正直なご意見を聞くことが多い。しかし筆者は特に、多くの患者さんの治療を行った経験が充分でない若い先生方には、大規模臨床試験の結果をよく読み、正しく理解し、重視して臨床に適用してほしい、と言っている。

筆者は clinical epidemiology、あるいは pharmaco-epidemiology の教えることは4つのP、だと捉えている。それらは、prevalence、 prediction, prevention, promotion である。例えば、本邦で2型糖尿病患者200人を5年間治療していると、たとえ良好な血糖コントロール状況に維持したとしても、9人が脳卒中を、さらに異なる10人が心筋梗塞を発症する、これほどの prevalence であることを JDCStudy は示している。さらに、どのような患者が心筋梗塞を起こしたのか、その予知因子は何であったのか、を遡って解析し、教えてくれる。最も大切なことは、先人達の臨床知見を全て、今後来院する患者の preventing action に活かす、ことであろう。さらに、明白となった、優れた新しい治療方針を、一般診療に当てはめるべく、 Promotion すべきであろう。この 4P が日常診療に積極的に活かされなかったら、医療の進歩はない、と筆者は確信している。

JDCStudy のような素晴らしい研究成果を、あらゆる機会を通じて一般臨床医に普及させることこそが、われわれ専門医の責務であろう。翻って、多くの糖尿病患者を診ている私どもは同時に、自らの専門以外の多くの疾病の治療にも携わっていることになる。この際には、その疾病の“4P”を常に勉強し、実践しなければならない。若手医師のみならず私ども老年医師も勉強の毎日である。

事務局より

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横手幸太郎

千葉大学医学部附属病院では、現在２３名の患者さんのご協力を得て JDCS 研究に参加させていただいています。私個人としては今から 10 年前、先輩医師の手伝いでケースカードの記入などに携わったのが本研究との最初の出会いでした。電話による生活習慣指導など、その取り組みのユニークさを印象深く感じたことが記憶に残っています。その後、主として欧米を舞台に 2 型糖尿病患者の合併症予防における血糖や脂質への薬物介入あるいは包括的強化治療の有用性が次々と示され、またメタボリックシンドロームの概念が新たに登場するなど、生活習慣病領域における数多くのトピックスがありました。この期間に一致して、JDCS 研究がコホート研究としての性格を備え、世界的なトレンドに的確に対応し、時代が必要とする日本人エビデンスを次々に発信してきたことは 今更申し述べるまでもありません。と同時に、日本における多施設臨床研究がどうあるべきか？という一つのあり方を示して下さっていると感じ、山田信博先生、曽根博仁先生のリーダーシップ、センス、そしてご努力に 改めて感謝申し上げる次第です。

JDCS 研究は今後も大小血管障害のリスクに関する日本人のエビデンスを数多く生み出していくものと確信しますが、その実績を土台として、次に目指すべきものについても考える時期に来ているかも知れません。例えば本研究は、大血管障害のリスクとしてトリグリセライド（TG）の重要性を浮かび上がらせましたが、なぜ高 TG 血症が動脈硬化と関連するのか、そのメカニズムは未だ十分には解明されていません。また、TG や non-HDL コレステロールへの介入が真にイベントリスクを軽減できるのか、その場合、どのような手段による介入が最も有効か についてもエビデンスはありません。JDCS の財産を最大限に活かし、日本人糖尿病患者の予後改善に役立てるため、今後そのような部分にも貢献できれば幸せだと思います。

事務局より

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女子栄養大学 栄養クリニック所長
田中 明

私はJDCStudyの開始時から参加させていただいておりまして、初めは東京医科歯科大学第三内科、引き続いて同大学老年病内科の外来と、もう、13年目になりますでしょうか。開始時には80例で開始しましたが、死亡、転院などにより例数が減少して、現在60例の患者さんの経過をみております。20年以上私の外来に通われている患者さんも多く、患者さんの性格、家族や生活背景も熟知しており、糖尿病のコントロールはさぞ良好だと思われるでしょうが、実際には今ひとつというケースが多いのは糖尿病治療の難しさだと思います。糖尿病治療は患者さんにやる気を起こしてもらうことが最も重要ですが、最愛の娘さんの結婚、配偶者の死亡、仕事上の悩みなどの要因がやる気をなくさせてしまう、また、逆に、孫の誕生や仕事や趣味に生き甲斐を感じている時などには治療意欲も増してコントロールが良好になります。患者さんの治療意欲が低下している時に、治療の中断をしないように、なんとか良好なコントロールを維持できるように努力することが糖尿病専門医の仕事であると考えています。一方で、この10年余の間に糖尿病治療も大きな進歩を遂げたことも実感しております。超速効型や持効型インスリンの登場で、I型糖尿病例でも低血糖発作なしでHbA1c値6.5%未満のコントロールが可能になりました。また、SU薬やビグアナイドの他に新薬が次々と登場して経口薬治療の幅が大きく広がりました。このような治療手段の進歩は糖尿病診療全体の可能性を広げることにも貢献していると考えます。

JDCStudyが開始された頃は、日本人糖尿病に関する大規模試験は皆無であり、その結果については大いに興味を持ち、大きな成果を期待しました。そして、期待通り、山田信博先生、曽根博仁先生のご努力で、日本人糖尿病に関するエビデンスが次々と発表されていることはご承知の通りです。さらに、私からの要望ですが、JDCStudyで栄養関連のエビデンス作りも推進してほしいと言うことです。私は7年前から臨床栄養学に関わっておりますが、臨床栄養学のエビデンスが非常に少ないことを実感しております。今後、参加施設の栄養士を活用して食事摂取のより詳細な分析を行うことにより多くのエビデンスが作られることを期待しております。

事務局より

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JDCS ニュースレター

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櫻井 健一

JDC studyについては、大学院生の時からかかわらせて頂いています。当初、患者さんのご自宅に電話をかけさせていただくと説明すると皆さん驚いていたのを覚えています。外来の度に電話でどのようなお話をされたか報告してくださる方もいました。一定期間が過ぎ、電話での指導が終了するころには患者さんも寂しがっていたことも思い出されます。研究自体はその後も継続され、現在まで日本人2型糖尿病そのものや合併症における危険因子の特徴など多くの成果を出してきました。その間、病院を移られる患者さんもあり、なかなかフォローがままならないこともありました。そのような時に事務局の先生から安否だけでも確認してくださいとお電話を頂き、実際に多施設共同研究を運営していく先生方のご苦労がしのばれました。私自身も病院をうつられた患者さんに幾度となくお電話をする機会をもちました。幸いなことに、その都度お元気な声で近況を伝えて頂き、このような機会を持てることをうれしく思ったものです。

現在は、毎年の会議にも参加するようになり、この研究の成果を実際に解析された先生方から生の声でお聞きすることを楽しみにしています。実際解析途中の部分もあるとお伺いしており、今後どのような成果が出てくるかが楽しみです。糖尿病診療を考えてみると、細小血管症および大血管症の危険因子おのおのへの治療アプローチは増えてきており、今後も増えてくることと思います。治療を選択する場合に自分自身が納得できるとともに、その適切性・必要性を患者さんに説明しなければなりません。そのような場面でもJDC studyから得られた知見は力を発揮してくれます。海外のデータではなく日本人から得られたデータは患者さんにとっても納得のいくものと思われます。

JDC studyのようなコホート研究は継続することにより多くの知見が得られますが、継続すること自体が困難であることもまた事実だと思います。今後もこの研究が継続され、日本人2型糖尿病に関し新しい知見を見出していくことを期待すると同時に、そのような研究にかかわれることを幸せに感じています。

事務局より

本年もどうぞよろしくお願い申し上げます。
今月1月27日に班会議を予定しております。年度末のお忙しい時期とは存じますがご出席の先生方におかれましてはどうぞよろしくお願い申し上げます。

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